REMARKS

Antecedent support for the method defined in new claims 403-405 is found in the specification at pages 20, 21, 31, 32, 33, 35, 37, 43-56 and 62 (including Examples 18, 19 and 36). One skilled in the art reading the specification would readily understand that the embodiments of Examples 18, 19, and 36 are merely exemplary of the use of growth factors in general and that Applicant was in possession of using stem cells as alternative embodiments to using nucleic acid growth factors.

Claims 383, 384, 391, 393, and 394 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite; and claims 382-402 were rejected under U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Reconsideration of such rejections is requested in view of the following remarks and associated evidence.

The rejection of claims 383, 384, 391, 393, and 394 is understood to be on the basis that the term "multifactorial and non-specific" is indefinite. Applicant disagrees that said claims fail to satisfy the "definiteness" requirement of the statute and proffers the following remarks and evidence in rebuttal.

Applicant remains confounded as to why this ground of the rejection was made and maintained (for reasons that have continued to shift during the course of this prosecution, including the present Office Action) because such rejection is inconsistent with a prior Patent and Trademark Office (hereinafter referred to as "PTO") decision. The Examiner has merely stated that it is not the policy of the PTO to perpetuate errors yet did not identify or discuss any errors in the prior PTO determination. Rather, it appears that the respective Examiners

considered Applicant's disclosure and reached differing opinions and understandings regarding the terms "multifactorial" and "non-specific." Thus, the Examiner appears to be challenging a prior PTO determination on the basis of mere opinion rather than presenting objective evidence. Accordingly, it appears that the Examiner's challenge to the determination of the prior Examiner amounts to no more than second guessing such determination. If such practice were to be condoned, the presumption of validity attached to an issued patent would be seriously eroded.

In connection with the above-mentioned challenge, the Examiner stated at page 4 of the present Office Action, "When issues are first identified, they must be raised." The basis for such statement is obscure. Is the Examiner stating or implying that the prior Examiner neglected to consider whether such term is definite and understood by those skilled in the art? If so, such statement requires verification that the prior Examiner never considered whether or not the terms were definite. In the absence of verification, the statement appears to be an attempt by the current Examiner to speak on behalf of the prior Examiner and does not constitute evidence that the prior Examiner committed error. Thus, the Examiner appears to be merely substituting her opinion for that of the prior Examiner.

A further aspect regarding the prior Examiner's determination is that such determination, in and of itself, constitutes strong evidence that the terms are understood by those skilled in the art. The Examiner did not address such point in the present Office Action. When this evidence is taken in combination with the evidence presented by Applicant below, including that presented by two highly skilled physicians, there should be no doubt that one skilled in the art would

understand such terms and that claims 383, 384, 393, and 394 are definite within the meaning of the second paragraph of 35 U.S.C. §112.

It is again pointed out for the record that claims 13 and 26 of Applicant's Patent No. 5,759,033 (enclosed herewith as Exhibit A and hereinafter referred to as "the '033 patent") specify that the claimed growth factor is multifactorial and non-specific. The grant of these claims by the PTO constitutes compelling evidence that the disputed terms are statutorily definite.

Independent evidence supporting the prior PTO decision may be found in the results of Applicant's search, using the Google search engine, for the term "multifactorial growth factor." Several publications were located using the questioned term to describe growth factors. In this regard, J. Biol. Chem, Vol. 280, August 5, 2005 (Exhibit A to the Amendment of June 26, 2006) relates to using the integrative nuclear fibroblast multifactorial growth factor FGFR 1. Furthermore, J. Eukaryot Microbiol, 49(5), 2002, pages 383-390 (Exhibit B of the Amendment of June 26, 2006) discloses that epidermal growth factor (EGF) is a multifactorial growth factor that activates signal transduction events in mammalian cells. Both fibroblast (FGF) and epidermal (EGF) growth factors are described as multifactorial growth factors capable of promoting the growth of soft tissue in the body of the patient on pages 20 and 21 of the specification. If such growth factor species are described as "multifactorial," then it is incumbent upon the Examiner to explain why other growth factor species, such as cells, would not also be so described. In other words, if the Examiner understands the meaning of "multifactorial" for one species of growth factor, then persons of ordinary skill in the art as well

as the Examiner should be capable of understanding the meaning of "multifactorial" for all other species of growth factors.

Applicant is aware that a portion of the Examiner's position involves whether or not cells can be described to be multifactorial. Inasmuch as the Examiner already has acknowledged that cells are growth factors, Applicant can find no apparent reason why the Examiner should continue to assert that cellular growth factors, unlike other growth factors, would not be described as multifactorial in view of the publications cited in the previous paragraph and Applicant's specification at page 21, lines 14 and 15, which describes the genus "growth factor" as multifactorial and non-specific. In the present Office Action, the Examiner has not addressed this point or explained why a cell would not be so described. It is puzzling to Applicant that the Examiner, at page 6 of the present Office Action, stated in connection with the term multifactorial that, "It is used to describe a cause (for example, of the disease) or an effect (for example, of the genes)." (emphasis added) and yet apparently fails to understand the term. If the Examiner can understand the underscored passage for a gene, how can she fail to understand such underscored passage as it pertains to other growth factors such as cells? To reach the Examiner's conclusion, it is necessary to disregard disclosure regarding growth factors and to selectively ascribe such disclosure to only a certain species, i.e., genes, of growth factors. The Examiner has presented no evidence to support such selective interpretation.

Applicant again directs the Examiner's attention to the recent *en banc* decision of the CAFC in Phillips v. AWH Corporation, 03-1269-1286, decided July 12, 2005. While the Phillips case involved patent claim infringement, Applicant believes that the principles and

authorities expressed in this case are equally applicable for providing guidance to the PTO in determining the meaning of terms in the specification and claims of a pending patent application.

The Phillips decision indicated that the claims of a patent are generally given their ordinary and customary meaning in the art, citing the Vitronics v. Conceptronic, Inc., 90 F. 3d 1582 (Fed. Cir. 1996). Also cited was the Multiform Desiccants, Inc. v. Medzorn, Ltd. Decision, 133 F. 3d 1473, 1477 (Fed. Cir. 1980) for the principle that claims should be read in the context of the patent. The Court in Phillips further observed that extrinsic evidence is less significant than the intrinsic record in determining the legally operative meaning of claim language, citing C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F. 3d 858, 862 (Fed. Cir. 2000). The Court in Phillips also stated that dictionary evidence can be useful in claim interpretation but that such evidence is less reliable than the patent specification and its prosecution history. Applicant submits that the Examiner should interpret the words "multifactorial" and "non-specific" in light of the specification as would be apparent to a person skilled in the medical art and thus give such words their ordinary meaning in the art to which the invention pertains. A different interpretation, such as that foisted by the Examiner, bottomed on non-contextual sources, places the term out of context and thus clearly would not be entitled to the same evidentiary weight as the interpretation by a skilled person in the medical art being appraised of Applicant's disclosure.

The Examiner purports to follow the tenants of Phillips but still apparently does not understand the disputed terms. As will be evident later, the Examiner did not follow the instructions of Phillips regarding a skilled medical person's understanding of the specification. The lack of understanding of the disputed medical terminology appears to be that of the

Examiner, not of those skilled in the art. Had the Examiner appreciated that the specification is directed to growth factors and that a cell is a growth factor specie, an appropriate search would have indicated, and the Examiner would have become aware, that the art uses the term "multifactorial" in connection with growth factors. Instead, the Examiner ignored the specific disclosure of the specification and conducted a series of non-contextual searches, thereby ignoring the import of Phillips.

The above point is underscored by the various searches performed and discussed on page 5 of the present Office Action. It appears that the Examiner has gone to great lengths to conduct searches in areas not related to Applicant's disclosure and has obtained results also not related to Applicant's disclosure and claims. This procedure ignores Applicant's previously presented contextual search results directed to the multifactorial growth factors disclosed in the specification. The Examiner did not explain why the results of Applicant's search were not considered to be persuasive and instead relied upon her other searches. Once again, the Examiner has ignored contextual search results of Applicant and wandered from the context of Applicant's specification. The Examiner should instead focus upon the present invention, as described in the specification, and consider and understand the fact that a cell is a species of growth factor and then consider the highly relevant search evidence presented by Applicant.

Whether the disputed terms encompass cells other than stem cells and germinal cells is not relevant to the issue of definiteness. Rather, stem cells and germinal cells are simply examples of cells possessing such characteristics.

Further, at page 5 of the present Office Action, the Examiner apparently is not familiar with the medical term "cascade of genetic material" because the meaning of such well-known and established medical terminology was questioned and obviously not understood. In response to the Examiner's questioning of the term "cascade of genetic material" and the Examiner's opinion that such language "makes no sense," Applicant makes the following points. First, such question is irrelevant to the definiteness rejection because the questioned language does not appear in the claims. Second, technical language that is not understood by a layman often makes sense to those skilled in the art. Third, the questioned terminology is commonly employed in the medical art and is well understood by those skilled in the art. For example, use of the questioned terminology may be found in an article published in 2001 by the American Heart Association, entitled, "Tubes, Branches, and Pillars," authored by Hellmut G. Augustin, and attached hereto as Exhibit B. The term "angiogenic cascade" is set forth in the first paragraph of this article. Another use of the questioned terminology may be found on website of the University of Pittsburgh, Department of Molecular Genetics and Biochemistry, regarding Nathan Bahary, M.D., Ph.D., at http://www.mgb.pitt.edu/personnnel/Bahary_Nathan.htm. The term "genetic cascade" is used in connection with vasculogenesis in the first paragraph of the second page. A copy of information from such website is attached hereto as Exhibit C. Clearly, if one misunderstands a basic medical term, i.e., "genetic cascade," any interpretation of "multifactorial" and "non-specific" based upon such misunderstanding lacks a sound foundation.

As mentioned above, the Examiner attempts to support her reasoning by a lack of success in regard to search results for the term "multifactorial and non-specific cell," followed by

a series of suppositions and speculations regarding the meaning of these terms. As demonstrated above, the Examiner's failed search appears to have been improperly and erroneously conducted and certainly does not support the Examiner's position. Thus, Applicant believes that the Examiner's position amounts to no more than opinion because no meaningful objective evidence, such as why cells would not be multifactorial and non-specific when other growth factors are acknowledged to be multifactorial and non-specific, is presented. Had the Examiner viewed the terms "factor," "multifactorial," and "non-specific," as understood by a skilled medical person and in the context of the specification, the issue of indefiniteness would not have been raised. The meaning of the term "factor" is well known in the medical art, and one skilled in such art would have no difficulty understanding this term. Obviously, anyone understanding the medical term "factor" would also understand the term "multifactorial" to mean "more than one factor."

The Examiner is reminded that Applicant previously located and filed relevant search evidence in the Fifth Supplemental Information Disclosure Statement ("IDS") filed on October 21, 2004, via fax, regarding the definitions of the questioned terms. The definitions of "multifactorial" and "non-specific" presented in the IDS provide confirming evidence that the disputed terms are known and used properly in Applicant's specification. Note further that the IDS identifies these term as adjectives.

Applicant also reminds the Examiner that a search of the NIH Medical Dictionary was conducted by Applicant and is of record. The following definitions in Merriam Webster's Medline Plus Medical Dictionary were found:

Factor:	***(noun)*** A substance that functions in or promotes the function of a particular physiological process or bodily system.
Multifactorial:	***(adjective)*** Having, involving, or produced by a variety of elements or causes.

Thus, the noun "factor," as used in Applicant's specification, means a substance, such as a cell, that promotes a particular physiological process, such as the formation of a bud, and subsequent growth of soft tissue. Such definition does not describe a factor as a process, as erroneously understood and then alleged by the Examiner. "Multifactorial" is an adjective used to denote a quality of a cell. In the context of Applicant's specification, a cell is deemed to be "multifactorial" when a variety (more than one) of elements (factors) promote the growth of soft tissue. Accordingly, there can be no doubt that the term "multifactorial" is used properly in the specification and that its meaning would be clear to one skilled in the medical art. Note again that in connection with the term multifactorial, the Examiner acknowledged by stating at page 7 of the present Office Action that, "It is used to describe a cause (for example, of the disease) or <u>an effect (for example, of the genes)."</u> (emphasis added). However, the Examiner somehow continues to fail to understand the term, despite the fact that the above underscored passage is consistent with the above definitions provided by Applicant. The above-mentioned definitions are consistent with Applicant's specification; with the materials furnished in the IDS; with the use of this term by those skilled in the medical art, such as Drs. Heuser and Lorincz; and with the previous determination of the PTO.

The questioned terms were "read and understood" by skilled persons in the art, i.e., by Dr. Heuser in his Declaration (of record) and in his Second Supplemental Declaration (attached as Exhibit C to the Amendment of June 26, 2006) and by Dr. Lorincz in his Supplemental Declaration (of record) and in his Second Supplemental Declaration (attached as Exhibit D to the Amendment of June 26, 2006). The Examiner criticized such evidence, as it pertained to Dr. Heuser's Declaration and Dr. Lorincz' Supplemental Declaration, at page 8 of the present Office Action because "they do not explain what cells are encompassed by the term." Such criticism misses the point because it is clear that the terms were read and obviously understood by these two experts in the medical art, thereby showing that the terms are, in fact, definite. It is noted that all of the above-mentioned declarations state that relevant portions of the specification regarding multifactorial and non-specific cells were "read and understood" by Drs. Heuser and Lorincz, thereby further underscoring that such terms are understood by those skilled in the medical art. Surely, the Examiner does not contend that such experts do not understand the disputed terms. It appears that the Examiner has continued to ignore such compelling evidence and merely substituted her opinion instead.

The Examiner is reminded that Applicant's specification indicates that multifactorial and non-specific cells may include stem cells and germinal cells. The Examiner has concocted an issue that other cells are not mentioned. Initially, the Examiner erroneously raised the issue that only stem cells were included. Upon Applicant pointing out that germinal cells were also included in the specification, the Examiner then changed the issue to what further cell types were included. Applicant believes that the disclosure of the above-mentioned two types of

multifactorial and non-specific cells, along with pluripotent and bone marrow stem cells, is fully adequate to describe examples of types of cells having the described characteristics to one skilled in the art. Applicant points out further that the number of cells that may be multifactorial and non-specific is not relevant to the understanding and definiteness of these disputed terms.

Another example supporting the definiteness of the questioned terms by workers skilled in the medical art that is consistent with the description in Applicant's specification, the definition of "multifactorial" in the IDS, the above-mentioned NIH Medical Dictionary, and Drs. Heuser and Lorincz, is be found in Strauer 2005 (of record). Dr. Strauer states at page 1656, second column, third paragraph that, "The regenerative potential of bone-marrow-derived stem cells may be explained by any of four mechanisms." These four-cell biologic and molecular mechanisms are further described as "factors" at page 1657, second column, second full paragraph. Therefore, it is clear to a skilled person in the medical art that Dr. Strauer and his co-authors identify the regenerative potential of bone marrow stem cells as being derived from at least four different mechanisms/factors or characteristics of such cells. It follows that bone marrow stem cells can be appropriately styled as four-factor cells, i.e., multifactorial. Thus, Strauer 2005 confirms that yet another skilled group of medical experts possesses an understanding of "multifactorial" cells that is consistent with that of Applicant, the evidentiary materials discussed herein, and the prior PTO determination.

In the present Office Action at page 9, the Examiner considered that, "Even if Strauer 2005 could be <u>tortuously construed</u> as describing bone marrow stem cells as multifactorial, Strauer 2005 only discusses bone marrow stem cells (emphasis added)." Note further that

Applicant describes using the same stem cells as Strauer 2005–bone marrow stem cells. Whether characterized as tortuous or being clearly evident to one skilled in the medical art, the fact remains that Strauer 2005 fairly and reasonably teaches that a type of stem cells are multifactorial and thus supports Applicant's position. It would seem to Applicant that the Examiner's acknowledgement in the above quoted passage should serve to conclusively resolve this issue. Also at page 9 of the present Office Action, the Examiner stated that, "Strauer 2005 uses 'four mechanisms' to describe regenerative potential," not the cells *per se*. Whether or not Strauer 2005 is limited to describing bone marrow cells as "multifactorial" misses the issue of whether one skilled in the art would understand the meaning of the disputed terms. If such term is acknowledged to be understood for growth factors (see Applicant's above discussed search results) and for bone marrow stem cells (see the Examiner's above acknowledgement), how can there be any remaining doubt as to the meaning of the term?

For the record, the Examiner's attention is again directed to yet another publication in which a skilled medical person utilizes the term "multifactorial" in a manner consistent with Applicant's specification; namely, the 2001 publication of Caplan et al. (attached as Exhibit E to the Amendment of June 26, 2006 and hereinafter "Caplan 2001") entitled, "Mesenchymal stem cells: building blocks for molecular medicine in the 21st century." Note the use of the term "multifactorial" in this publication. Caplan 2001 teaches that mesenchymal stem cells prevalent in bone marrow are pluripotent in that they are capable of differentiating into multiple tissues types. Caplan 2001 further teaches that such bone marrow stem cells undergo multifactorial differentiation pathway from stem cells to functional tissues including elaborate composite

tissues *in situ*. This description is consistent with Applicant's use of the terms "multifactorial" and "non-specific" to define pluripotent cells such as bone marrow stem cells and germinal cells, which induce or promote the growth of composite soft tissues. The Examiner took issue with Caplan 2001 by stating that this publication describes a process. Such position ignores the above-presented definition of a factor.

In the Sixth Supplemental Information Disclosure Statement (of record), Applicant also submitted an earlier publication of Caplan, namely, a publication entitled "Mesenchymal Stem Cells," Journal of Orthopaedic Research, Volume 9, No. 5, 1991, pages 641-650 (hereinafter "Caplan 1991"). Caplan 1991 describes bone marrow stem cells as exhibiting multifactorial characteristics. Accordingly, Applicant believes that Caplan 1991, like Caplan 2001, contains compelling evidence that those skilled in the medical art understand and use the questioned terms in a manner consistent with Applicant's use thereof. Caplan 1991 described mesenchymal stem cells ("MSC"), which were harvested from bone marrow and/or periosteum, as comprising multifactorial cells. Specific passages of Caplan 1991 are referenced below in support of Applicant's position.

Regarding Applicant's use of the term "multifactorial cells," which cells are species of the described and claimed genus "growth factor," Caplan 1991 recognized and attributed multifactorial characteristics to MSC at page 641, left column paragraph 1, lines 8-14 and at the top of page summary, lines 6-8.

The first reference at page 641 is as follows:

> Their progeny are affected by a number of factors, however, as they become tracked into very specific

> developmental pathways in which both intrinsic and extrinsic factors combine to control the molecular and cellular pattern of expression that results in specific tissues that perform specific functions based on their molecular repertoire (9,11).

The second reference at page 641 is as follows:

> Local cuing (extrinsic factors) and the genomic potential (intrinsic factors) interact at each lineage step to control the rate and characteristic phenotype of the cells of the emerging tissue.

As should be understood by the Examiner and any skilled person in the medical art, Caplan 1991 clearly characterizes MSC as multifactorial cells because more than one factor is described; and thus no issue regarding the meaning of "multifactorial" should remain.

Applicant's search also revealed the Merck Manual of Geriatrics, Ch. 72, Cancer (attached as Exhibit F in the Amendment of June 26, 2006), which describes "Oprelvekin, a nonspecific growth factor for megakaryocytes" and the NIH Pub Med abstract identifying "Erythropoietin as a nonspecific growth factor and its effect on carcionogenesis" (attached as Exhibit G in the Amendment of June 26, 2006). Regarding the limitation "non-specific" cells, species of the genus "growth factor," Caplan 1991 disclosed that MSC are lineage-nonspecific, i.e., they can develop into nine (9) separate and unique tissues. In this regard, see Fig.1. page 642. Thus, it is patently clear that the art skilled understand the meaning of the term "non-specific" when applied to cells such as stem cells - they are lineage-nonspecific and can develop into a variety of tissues. For the Examiner to deny this fact requires a denial of pure science, and there can be no further issue regarding the understanding of such term by one skilled in the medical art.

It is submitted that Applicant's above-mentioned evidence, when considered with the authoritative statements and precedential tenets of Phillips, must be accorded far greater evidentiary weight than the Examiner's unsubstantiated speculation as to the intended meaning of the questioned term. When following the Phillips decision and thus reading the claim language within the context of the specification with the understanding of a person skilled in the medical art, Applicant believes that there can be no question as to the meaning of "multifactorial." The meaning of "non-specific" as being synonymous with "non-specialized" is apparent from previous submissions and the above-mentioned evidence.

When it is considered that the PTO previously determined – and obviously believed – that the questioned terms are definite, that Drs. Heuser and Lorincz read and understood such terminology, and that Applicant presented a large body of independent evidence supporting, and consistent with, the prior determination of the PTO and Applicant's medical experts, it appears that the Examiner is the only one that does not understand such terms. Surely, the Examiner's opinion and stated lack of understanding of such medical terminology cannot overcome such compelling evidence. Accordingly, this aspect of the indefiniteness rejection should be withdrawn.

Applicant submits that the Examiner erred in concluding that claims 383 and 384 are contradictory. Claim 383 requires "multifactorial and non-specific cells." Claim 384 further limits claim 383 by reciting that the cells are "stem cells." The specification at page 37 describes stem cells and germinal cells as included in the class multifactorial and non-specific, and at page 50 further describes multifactorial and non-specific growth factors, such as the "stem cells and

germinal cells" described on page 37, as being "pluripotent." Accordingly, it requires no more than a basic understanding of patent claim construction to conclude that claim 384 is in full compliance with the fourth paragraph of Section 112. Further, it is noted that the Examiner queried at page 11 of the present Office Action that, "is Applicant implying that not all stem cells are multifactorial and non-specific?" The answer to such query is "no" because not all stem cells are multifactorial and non-specific. Applicant repeats the well-known and well-established fact that not all stem cells are multifactorial and non-specific. Any skilled person in the medical art would readily understand and agree with such fact. Claim 394 is deemed proper since it further limits claims 393 and 391, from which it directly and indirectly depends. Such limitation is proper because claim 391 broadly includes both single factorial and multifactorial cells, and dependent claim 393 further limits such cells to multifactorial cells. The specification on page 48 clearly discloses that, "germinal cells (and in some cases, stem cells,)" can result in growth and differentiation of an organ. This is a clear teaching that not all stem cells result in morphogenesis. Thusly, Applicant's specification clearly discloses that, to one skilled in the medical art, while multifactorial and non-specific cells are types of stem cells, not all stem cells are multifactorial and non-specific.

In summary, Applicant believes that once the Examiner's misunderstanding of the questioned terminology is transformed into an understanding consistent with that used by a skilled person in the medical art, there should be no further question of definiteness remaining. Applicant hereby repeats the remarks (and associated evidence) that were presented in the August 2, 2005 Response and in the June 26, 2006 Amendment. These remarks are incorporated

into the instant response so as to not further burden the record. However, such remarks are consistent with the above remarks and are maintained, are continued to be relied upon, and are deemed to be persuasive. Applicant submits for all of the above reasons that claims 383, 384, 391, 393, and 394 are in compliance with the definiteness requirement of the statute and that the Examiner's rejection should be withdrawn.

Claims 382-402 stand rejected under 35 U.S.C. §112, first paragraph, for failure to satisfy the written description requirement of the statute. The Examiner's rejection, which is bottomed on the belief that the claim requires the formation of "one tissue" and that the instant specification "does not appear to have support for formation of one tissue to the exclusion of others by administration of cells," appears to be based on a misunderstanding of Applicant's claimed and disclosed invention.

Lest there be any doubt as to Applicant's disclosed and claimed invention, Applicant has amended claim 382 by deleting the word "a" prior to "desired soft tissue" at line 1. Although Applicant believes that, prior to such amendment, claim 382 was readable upon more than one soft tissue, deletion of the word "a" removes any doubt that the claim is readable upon more than one soft tissue. Applicant's specification discloses growing two general types of tissue in the human body – soft and hard. The broadest statement of Applicant's invention is found on page 20 of the specification and clearly describes using the genus "growth factors" to grow either soft or hard tissues in the body of a human patient. The term "soft tissue" is well understood by those skilled in the medical arts to broadly include fat, fibrous tissue, blood vessels, and other supporting tissue of the body. The specification's use of the term "soft tissue" is consistent with

its ordinary meaning in the art. The specification discloses that stem cells grow tissues and organs through morphogenesis and differentiation. The specification on page 33 describes morphogenesis as the growth and differentiation of cells and tissues during development of an organ. The Examiner has acknowledged that cells, i.e., stem cells, are species of growth factors and for good reason. The specification is replete with the description of using growth factors for growing either hard tissue such as bone or soft tissue such as arteries. The specification on page 40-44 discloses that stem cells, such as bone marrow stem cells, differentiate during morphogenesis to form composite soft tissue structures. The specification on page 44 describes an organ as "consist-[ing] of two or more kinds of tissues joined into one structure…" The specification on page 45 discloses, "An artery is an organ of the circulatory system." The specification on page 46 discloses that cells are used to grow new muscle and new arteries. The specification on page 47 teaches that reimplantation of a patient's own cells can be used to grow organs, sub-organs, and tissues; and on page 48 teaches that when reimplanting a patient's own germinal cells or stem cells that organs or function specific tissues are formed via differentiation and morphogenesis. Prophetic examples 18 and 19 describe and enable using growth factors for growing arteries in the leg and heart of a human patient. One skilled in the medical art appraised of the teachings in the specification would readily understand that Applicant was in possession of the novel process of using growth factors, including stem cells for growing desired soft tissue, such as an artery, as called for in the instant claims. The Federal Circuit has "…repeatedly rejected the contention that depiction of a single embodiment necessarily limits the claims to that depicted scope." Afga Corp. v. Creo Products, Inc., No. 05-1079. See also Phillips v. AWH

Corporation, supra. There is nothing improper in limiting claims to the use of cells as growth factors for growing only soft tissue. It is trite patent law that an applicant can claim less than he is entitled to by virtue of application disclosure. Applicant's intent in presenting claim 382 was to define a process wherein cells are used as growth factors for growing tissue consisting solely of soft tissue in the body of a human patient. This was Applicant's original intent and remains Applicant's intent to so claim the invention. Applicant believes that the Examiner's Section 112 lack of description (new matter) rejection lacks valid basis and should be withdrawn.

It is evident that the Examiner has failed to consider the disclosure provided by Applicant's specification as a whole in determining compliance with the written description requirement of the statute. The appropriate factual determination is whether the instant specification conveys to one skilled in the art that Applicant invented the claimed subject matter. The Examiner erroneously restricted the factual determination to the elected species of growth factor and, thusly, ignored those portions of the specification describing a broader generic invention and also ignored description related to non-elected species. Applicant is entitled to have the entire disclosure considered in determining compliance with 35 U.S.C. §112, first paragraph. See In re Anderson, 471 F2d. 1237, 176 USPQ 331, (CCPA 1973). The selective, limited evaluation performed by the Examiner is clearly erroneous and fails to comport with current law. It is further apparent that the Examiner's evaluation is intended to be so limited in view of the Examiner's statement at page 6, lines 1-8 of the February 22, 2006, Office Action in co-pending application Serial No. 09/794,456. Such statement is set forth below.

> The issue here is not whether or not workers in this technology already knew the features of the cells recited in the claims; rather, the issue is that the instant specification did not set forth contemplation of a method step wherein cells were administered intravenously, intraluminally, or via angioplasty. As discussed in the previous paragraph, the instant specification did not set forth contemplation of such method steps. <u>The claims are being examined to the extent that they read on the elected invention, administration of cells, and thus the generic concept of growth factor is not relevant.</u> (emphasis added).

The reasoning in the above-quoted passage is remarkably similar to that in the instant rejection of claims requiring "injection" of stem cells and confirms the Examiner's erroneous construction of the written description. The Examiner's rejection appears to be bottomed on the ground that there is no "exemplification" of using stem cells to grow soft tissue (artery). As previously argued by Applicant, page 46 of the specification "exemplifies" using cells to grow soft tissue and the specification is replete with teachings of using stem cells for causing morphogenesis and growth of soft tissue (such as organs, i.e., arteries) in human patients. Therefore, Applicant's claims are in compliance with 35 U.S.C. §112, first paragraph, because the claims conform to what subject matter Applicant described as his invention in the specification. The first paragraph of Section 112 does not require a specific example of every embodiment within the scope of a broadly disclosed invention. See <u>In re Gay</u>, 399 F2d. 769, 135 USPQ 311 (CCPA 1962). The Examiner is apparently trying to limit Applicant's invention to the specific examples, notwithstanding the clear disclosure of a broader generic invention along with other non-elected species. The Examiner must focus upon the description of the generic invention and all species

falling under the genus when evaluating the content of the written disclosure. The Examiner has presented a distorted and inaccurate characterization of the invention by focusing only upon the descriptive material related solely to a single elected species. This is clear error. As may be observed, the examination of the elected species invention must include, and Applicant is entitled to, a fair and reasonable evaluation of the specification in its entirety.

Applicant submits that the Examiner's 37 CFR 1.75 (c) objection to claims 385-388, 390, and 392 is likewise groundless and should be withdrawn. The Examiner is correct in asserting that claim 382 is limited to growing soft tissue because this was Applicant's intent. The Examiner's statement that, "Claim 382 now appears to be limited to a single soft tissue type, rather than soft tissue comprising several different tissue types," however, is incorrect and evinces a misunderstanding of Applicant's invention. As pointed out above, for example, blood vessels such as arteries, are considered soft tissue in the medical arts. An artery is defined as an organ in the instant application and indisputably consists of two or three layers – an inner layer of endothelium, a middle layer of smooth muscle, and, in some cases, an outer layer of connective tissue. The Examiner has employed improper claim construction in determining the scope of Applicant's claims. The scope of claim 382 as amended, and before such amendment, broadly includes such soft tissue. Claim construction is legally based on the specification disclosure, not the Examiner's opinion. Should the PTO continue to take issue with such well-known facts then it is incumbent upon the Examiner to furnish <u>scientific evidence</u> in rebuttal thereof.

One final point remains. In the terminal paragraph of the Office Action, the Examiner

"puts" Applicant "on notice" that any attempt to claim a process for growing an artery "may cause reinstatement of the rejection over Lutjen et al." It is Applicant's prerogative to determine which claims shall be filed and pursued in seeking patent protection for his intellectual discoveries, not Examiner's. Further, Applicant submits that the outstanding Office Action is incomplete because the Examiner failed to consider the merits of all claims. For example, claim 402, when considering all the limitations thereof, defines a method for growing and integrating an artery into the leg of a human patient by intramuscularly injecting stem cells into said patient's leg. Does the Examiner contend that Lutjen et al.'s two-cell embryo implantation procedure responds to the claimed subject matter of claim 402 if presented in independent form?

From the foregoing remarks, Applicant submits that the instant application is in condition for allowance, and a Notice to such effect is respectfully requested. Should the Examiner have any questions or require additional information or discussion to place the application in condition for allowance, a phone call to the undersigned attorney would be appreciated.

Respectfully submitted,

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Circulation Research

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Editorials

Tubes, Branches, and Pillars

The Many Ways of Forming a New Vasculature

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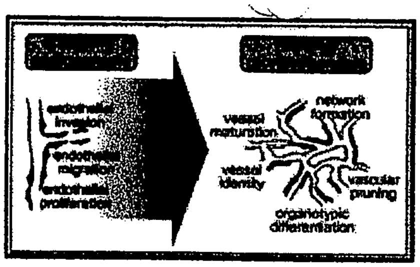
Key Words: angiogenesis • vasculogenesis • intussusception • intussusceptive microvascular growth

The angiogenic cascade is getting increasingly complex. A few years ago, vasculogenesis and angiogenesis were considered as the primary mechanisms leading to the formation of new blood vessels. The original definition of vasculogenesis denotes the formation of a primary embryonic vascular network from in situ differentiating angioblastic cells.[1] In contrast, angiogenesis primarily referred to the sprouting of blood vessels from preexisting vessels.[1]

Recent advances in the identification of molecules that regulate angiogenesis and vascular remodeling have shown that the simplistic model of an invading capillary sprout is not sufficient to appreciate the whole spectrum of morphogenic events that are required to form a neovascular network (Figure 1).[1–3] Undoubtedly, vascular endothelial growth factor (VEGF) acts at an early point in the hierarchical order of morphogenic events and probably fulfills all criteria to be considered as a master switch of the angiogenic cascade. In contrast, the angiopoietins and their receptor Tie-2 as well as the ephrins and their corresponding Eph receptors appear to act at a somewhat later stage of neovessel formation. These molecules orchestrate a number of related, yet functionally and molecularly not well understood, processes such as vessel assembly (network formation and formation of anastomoses), vessel maturation (recruitment of mural cells [pericytes and smooth muscle cells], and extracellular matrix assembly, pruning of the primary vascular bed), and acquisition of vessel identity (formation of arteries, capillaries, and veins)[3,4] (Figure 2). Lastly, the mechanisms of organotypic differentiation of the vascular tree (continuous endothelium, discontinuous endothelium, fenestrated endothelium) are not at all understood and the first molecules that govern subpopulation-specific vascular growth and differentiation are just being uncovered.[5,6]

Figure 1. Change of paradigm. From sprouting angiogenesis to vascular morphogenesis. Basement membrane degradation, directed endothelial cell migration, and proliferation (left) were considered as the primary



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mechanisms of angiogenesis. Corresponding in vitro assays have greatly helped to uncover molecules and mechanisms of angiogenesis. Today, the complexity of the sequential processes leading to the formation of a mature vascular network is increasingly recognized. These involve mechanisms of vessel assembly (network formation and formation of anastomoses), vessel maturation (pericyte recruitment, extracellular matrix assembly, pruning of neovasculature), acquisition of vessel identity (arteries, capillaries, veins), and organotypic differentiation (continuous endothelia, discontinuous endothelia, fenestrated endothelia). Yet, experimental systems to study these steps are largely missing.

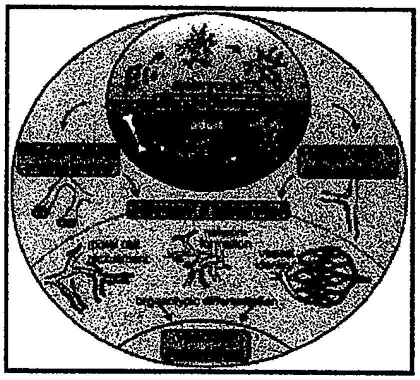

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Figure 2. Hierarchical order of morphogenic events during embryonic and adult growth of blood vessels. The primary formation of blood vessels occurs through mechanisms of vasculogenesis (center top). Vasculogenesis refers to the formation of a vascular network from precursor cells (angioblasts). Embryonic vasculogenesis results from the in situ coalescence of mesodermal angioblastic cells to form a capillary plexus. In contrast, adult vasculogenesis is mechanistically different and is mediated by the distal recruitment of angioblastic cells from precursor cell compartments (bone marrow). The secondary level of vascular morphogenesis describes the angiogenic formation of blood vessels. Angiogenesis refers to the formation of vessels and vascular networks from preexisting vascular structures (top, outer compartment). This can occur through classical sprouting angiogenesis with formation of anastomoses (top right) or through mechanisms of nonsprouting angiogenesis (top left). Nonsprouting angiogenesis occurs through mechanisms of intussusceptive microvascular growth (IMG) focally inserting a tissue pillar or by longitudinal fold-like splitting of a vessel. Sprouting angiogenesis and intussusception contribute to an increasing complexity of a growing vascular network. The network assembles and matures, eventually allowing directional blood flow. Cellular and biomechanical factors appear to be involved in shaping vascular identity (ie, arteries, capillaries, and veins), although there is also developmental biological evidence indicating that arteriovenous fate determination may occur before the formation of arteries and veins. Lastly, microenvironmental cues (extracellular matrix, cell contacts, and organ-selective growth factors) regulate the organotypic differentiation of a neovascular tree with continuous, discontinuous, and fenestrated endothelia. In contrast to the formation and maturation of new blood vessels through vasculogenic and angiogenic mechanisms, vascular remodeling describes the adaptational reorganization of an existing mature vasculature. This may occur acutely (eg, after sudden ischemia) or as a response to chronic stimuli (eg, atherosclerotic changes of vessel wall or in response to hypertensive biomechanical forces). The term "arteriogenesis" has been coined to describe the formation of collaterals from a preexisting capillary network after sudden ischemia as it occurs after cardiac ischemia or experimentally during surgically induced hindlimb ischemia. This process describes an adaptational remodeling phenomenon and should not be confused with the developmental acquisition of vessel identity that is associated with the formation of arteries, capillaries, and veins. Likewise, vessel cooption[18] describes a vascular remodeling phenomenon originating from an existing vasculature that may contribute to tumor vascularization.

The function of these molecules has largely been elucidated through genetic experiments in mice ablating or overexpressing individual molecules. Yet, a detailed understanding of their molecular and functional mode of action is missing, which is primarily due to the lack of appropriate in vivo and in vitro models in which to functionally study these molecules. Most in

vitro assays have very reductionist readouts such as endothelial cell chemoinvasion, migration, or proliferation. These assays have proven powerful in the early days of angiogenesis research. Yet, they are of limited use for the study of complex cellular interaction phenomena as they are associated with vessel assembly and vessel maturation. Likewise, most in vivo assays are either not quantitative or they are restricted to endpoint readouts that do not allow an appreciation of the dynamic three-dimensional spatiotemporal order of angiogenic processes, eg, in tumor models or in cardiac ischemia models. Most importantly, when it comes to studying angiogenesis in vivo, few laboratories apply three-dimensional techniques such as intravital microscopy or corrosion casting techniques to assess a neovascular bed. Instead, two-dimensional histological techniques are widely used to analyze angiogenesis in vivo. In fact, the counting of immunohistochemically stained microvessels in tissue specimens including tumors has become the gold standard to assess a neovascular bed in a given tissue.[7] Clearly, this reductionist analytical approach is by no means sufficient to realistically reflect the whole spectrum of three-dimensional morphogenic events dynamically over time.

It is primarily a consequence of the limited availability of appropriate experimental models and analytical tools that vascular network formation through the process of intussusception is still not widely appreciated. Intussusception or intussusceptive microvascular growth (IMG) describes the formation of a vascular network from an endothelial cell–lined vessel by focally inserting a tissue pillar or by longitudinal fold-like splitting of a vessel. As a consequence, IMG can result in complex vascular networks by a nonsprouting angiogenesis mechanism.[1,2]

The concept of vascular network formation through IMG is not new. Originally described more than 50 years ago,[8] analytical work on IMG was pioneered in the late 1980s and early 1990s by the Swiss anatomist Dr P.H. Burri.[9,10] This early work has clearly shown that IMG is an important nonsprouting angiogenesis mechanism that contributes to capillary network formation independent of classical sprouting angiogenesis (Figure 2). Physiologically, IMG occurs in a number of embryonic and adult tissues, most notably during embryonic vascularization of the lungs[11] as well as during the cyclic changes of the endometrial vasculature in the adult.[12]

In two studies published in this issue of *Circulation Research*, Dr Patan and colleagues[13,14] have shed further light into the complexity of intussusceptive microvascular growth. They have used the isolated mouse ovarian pedicle model to study IMG during wound healing–like granulation tissue formation and during growth of tumors grafted onto the ovarian pedicle. In this model, the ovarian vascular supply is surgically manipulated so that the isolated ovary is at the end of a pedicle that is supplied by the ovarian artery and the ovarian vein. This model was originally developed to perform hemodynamic studies in an experimental tumor that is supplied by a single feeding artery and a single collecting vein.[15] Patan et al have used this model to characterize the intussusceptive morphogenic remodeling of the ovarian vein and artery feeding into the granulation tissue[13] as well as into LS174T human colon adenocarcinoma growing in the isolated pedicle.[14] A zone of several millimeters was analyzed in both models through a carefully performed rather meticulous morphological analysis of several thousands of 2-μm serial sections. Computer-aided image analysis was then applied to three dimensionally reconstruct the vascular network. The results of both studies show quite clearly that IMG can lead to complex vascular networks completely independent of sprouting angiogenesis. Furthermore, the authors' high-resolution approach demonstrates how intussusceptive vascular folds organize to establish compound loop systems resulting from tissue segmentation and intussusceptive anastomoses.

As with any intriguing study, the experiments by Patan et al raise numerous additional questions. For example, what are the driving forces behind IMG? There is some evidence that the angiopoietin/Tie-2 ligand/receptor system is involved in controlling IMG.[16,17] Likewise, biomechanical forces may be involved in regulating IMG. The surgical manipulation in the ovarian pedicle procedure used by Patan et al[13,14] leads to significant changes in hemodynamic forces that may be involved in remodeling the preexisting ovarian vein as much as hemodynamic forces are believed to act as critical regulators of collateral formation following cardiac ischemia (arteriogenic vascular remodeling). This also raises the question of a zonal analysis of the observed intussusceptive morphogenic events, ie, does IMG occur in the center or in the periphery of the analyzed granulation tissue[13] and tumors?[14] Zonal analyses of vascular morphogenic processes are particularly relevant in the context of tumor angiogenesis. Microvessel counting studies usually quantitate intratumoral microvessel densities. Yet, the tumor periphery marks the invasive zone of a tumor and gives rise to metastatic cell dissemination. Thus, the equilibrium between tumor angiogenesis and remodeling of the preexisting vasculature in the tumor periphery (vessel cooption)[18] may be

very relevant in determining tumor fate. Lastly, and possibly most important, what is the quantitative contribution of IMG (and the other mechanisms of vessel formation) to neovascularization and particularly to tumor vascularization?

It is increasingly recognized that vascular morphogenesis is a complex process driven by a number of different mechanisms that can lead to the formation of endothelial cell-lined blood vessels. Figure 2 summarizes the hierarchical order of our present understanding of hemangiogenic morphogenic events (as opposed to lymphangiogenic processes). Future work in the field of angiogenesis research will need additional tools and models to systematically analyze angiogenic processes to fully understand the complexity of the angiogenic cascade. This will also include the implementation of more sophisticated invasive and noninvasive techniques to analyze the vasculature of human tumors. The elegant, yet cumbersome experimental, approach taken by Patan et al[13,14] clearly reflects our limited ability to appreciate angiogenesis as a dynamic three-dimensional process. The implementation of analytical techniques that systematically assess human tumor angiogenesis beyond the counting of microvessel densities is just at its beginning.[19] At the same time, novel angiogenic factors with a narrow cell and organ selectivity are being identified as inducers and modifiers of the angiogenic cascade.[5,6] Collectively, these observations indicate that the angiogenic cascade is far from being understood. Yet, a thorough understanding of the mechanisms of vascular morphogenesis will be a requisite for the rational translation of this knowledge into clinical application.

Footnotes

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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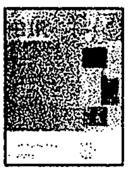

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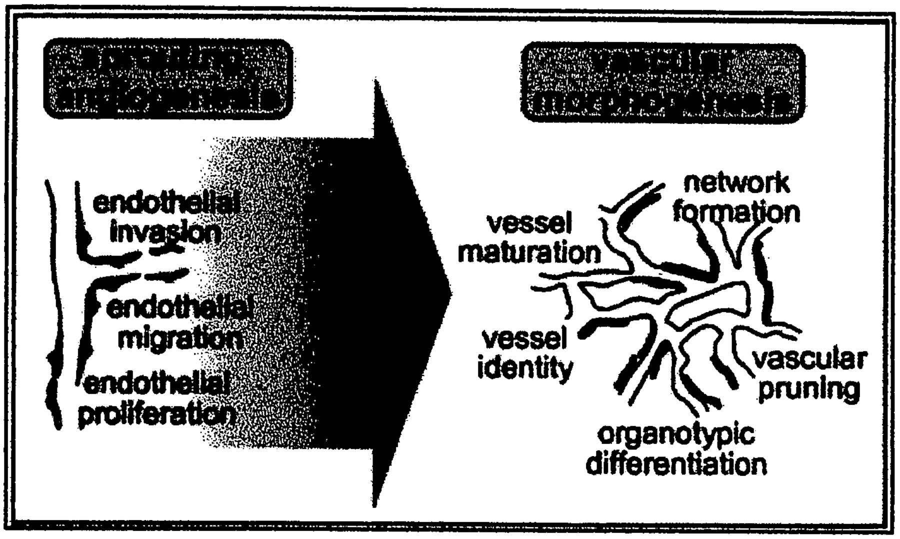

Figure 1. Change of paradigm. From sprouting angiogenesis to vascular morphogenesis. Basement membrane degradation, directed endothelial cell migration, and proliferation (left) were considered as the primary mechanisms of angiogenesis. Corresponding in vitro assays have greatly helped to uncover molecules and mechanisms of angiogenesis. Today, the complexity of the sequential processes leading to the formation of a mature vascular network is increasingly recognized. These involve mechanisms of vessel assembly (network formation and formation of anastomoses), vessel maturation (pericyte recruitment, extracellular matrix assembly, pruning of neovasculature), acquisition of vessel identity (arteries, capillaries, veins), and organotypic differentiation (continuous endothelia, discontinuous endothelia, fenestrated endothelia). Yet, experimental systems to study these steps are largely missing.

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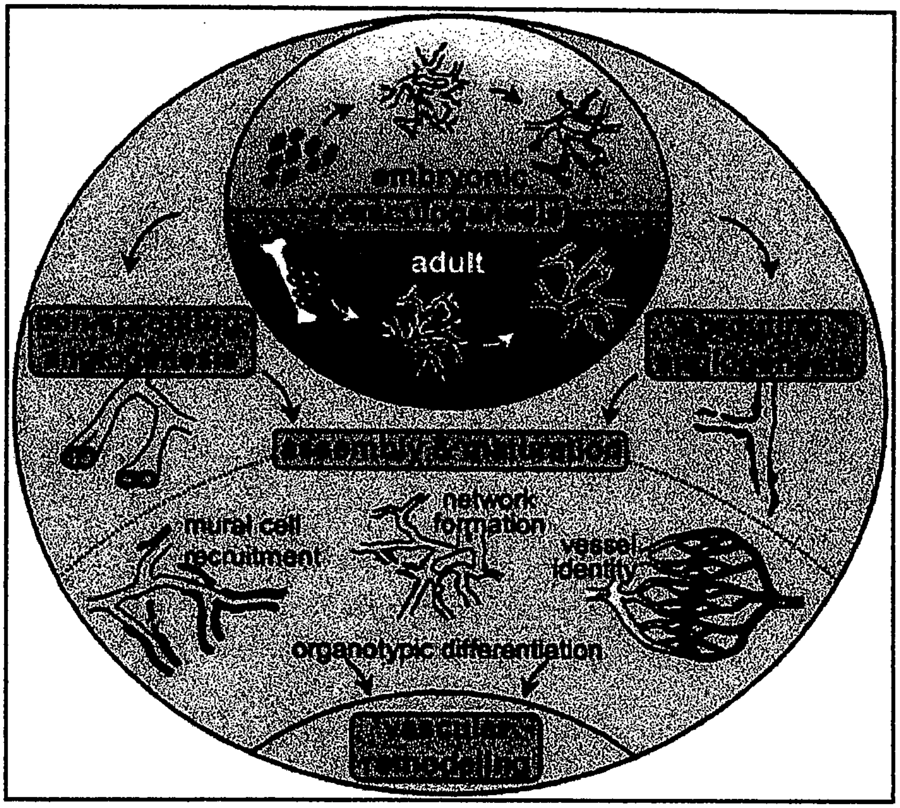

Figure 2. Hierarchical order of morphogenic events during embryonic and adult growth of blood vessels. The primary formation of blood vessels occurs through mechanisms of vasculogenesis (center top). Vasculogenesis refers to the formation of a vascular network from precursor cells (angioblasts). Embryonic vasculogenesis results from the in situ coalescence of mesodermal angioblastic cells to form a capillary plexus. In contrast, adult vasculogenesis is mechanistically different and is mediated by the distal recruitment of angioblastic cells from precursor cell compartments (bone marrow). The secondary level of vascular morphogenesis describes the angiogenic formation of blood vessels. Angiogenesis refers to the formation of vessels and vascular networks from preexisting vascular structures (top, outer compartment). This can occur through classical sprouting angiogenesis with formation of anastomoses (top right) or through mechanisms of nonsprouting angiogenesis (top left). Nonsprouting angiogenesis occurs through mechanisms of intussusceptive microvascular growth (IMG) focally inserting a tissue pillar or by longitudinal fold-like splitting of a vessel. Sprouting angiogenesis and intussusception contribute to an increasing complexity of a growing vascular network. The network assembles and matures, eventually allowing directional blood flow. Cellular and biomechanical factors appear to be involved in shaping vascular identity (ie, arteries, capillaries, and veins), although there is also developmental biological evidence indicating that arteriovenous fate determination may occur before the formation of arteries and veins. Lastly, microenvironmental cues (extracellular matrix, cell contacts, and organ-selective growth factors) regulate the organotypic differentiation of a neovascular tree with continuous, discontinuous, and fenestrated endothelia. In contrast to the formation and maturation of new blood vessels through vasculogenic and angiogenic mechanisms, vascular remodeling describes the adaptational reorganization of an existing mature vasculature. This may occur acutely (eg, after sudden ischemia) or as a response to chronic stimuli (eg, atherosclerotic changes of vessel wall or in

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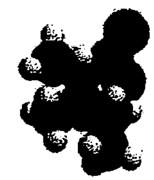

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The principal theme of my research interests is to combine the power and insight of vertebrate development to elucidate basic molecular processes. Many of the genes involved in normal vertebrate development processes have been implicated in the causative pathway of human diseases. Thus, an understanding of normal developmental processes can be a key initial step toward fundamental advances in understanding and treating human disease. One of the methods used to characterize the discrete steps involved in normal vertebrate development is the generation of mutants and alteration of specific gene expression. In this regard, the zebrafish (Danio rerio) is an especially robust vertebrate system for isolating and defining the novel factors affecting these processes. The developing embryos are transparent, facilitating visualization, and have functioning organ systems by 24 hours post fertilization. Mutagenesis screens have

defined many ENU (which induces point mutations in DNA), gamma and insertional mutants whose defective gene functions can be described and investigated by many techniques, and isolated by genetic means.

My lab is focused on utilizing functional genomics and forward genetic screens in the zebrafish to help delineate basic aspects of vasculogenesis, hematopoiesis and gastrointestinal development and reaction of these tissues to injury. For instance, the zebrafish mutant *cloche* has a combination of hematopoietic, vascular and lymphoid defects which suggest that the *cloche* gene product is critical to the function of the hemangioblast. Characterizing and cloning this mutation will facilitate unique insights into the genetic cascade that regulates hematopoiesis and vasculogenesis.

In contrast to our depth of knowledge into various aspects of hematopoiesis and vasculogenesis there is a poor understanding on a molecular level of epithelial (including gastrointestinal) development/regeneration and gastrointestinal tumors. This paucity of knowledge has paralleled the lack of insight into the specific steps involved in the normal differentiation and patterning of the gastrointestinal system needed to base our understanding of the disease states. In my lab, transgenic zebrafish, made by fusing the promoter elements of gastrointestinal specific genes with a fluorescent marker (GFP) are being made to help elucidate the key steps in gastrointestinal development. Additionally, in-situ hybridization of genes from specific cDNA libraries is being done to analyze their temporal-spatial expression. Using a variety of techniques available in the zebrafish, such as over/misimpression, morpholino antisense RNA knockdown and the development of new transgenics, the normal function of these genes, and their possible roles in disease states can be elucidated. ENU mutagenesis in the zebrafish is also being utilized to screen for zebrafish with mutations in gastrointestinal development. Zebrafish harboring these mutations can be identified by loss of GFP expression in the transgenic fish, or by in-situ hybridization and morphology in non-transgenics.

Together, this work will help elucidate the pathways involved in normal hematopoiesis, vasculogenesis and gastrointestinal development with the

emphasis on providing the basis for designing rational, molecularly based disease directed therapies.

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